robotically assaying a plurality of synthetic compounds corresponding to at least some of said virtual compounds for one or more desired physical, chemical or biological properties by computer-controlled real-time polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

57. (New Claim) A method of defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid sequence comprising:

robotically synthesizing a plurality of synthetic compounds; and

robotically assaying said plurality of synthetic compounds for one or more desired physical, chemical or biological properties by computer-controlled real-time polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

58. (New Claim) A method of defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid sequence comprising:

generating a library of nucleobase sequences *in silico* according to defined criteria; and

robotically assaying a plurality of synthetic compounds having at least some of said nucleobase sequences for one or more desired physical, chemical or biological properties by computer-controlled real-time polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

59. (New claim) A method of defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid sequence comprising:

evaluating *in silico* a plurality of virtual compounds according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically assaying a plurality of synthetic compounds corresponding to at least some of said virtual compounds for one or more desired physical, chemical or biological properties.

60. (New Claim) A method of generating a set of oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to defined criteria; and

c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled real-time polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

61. (New Claim) The method of claim 60 wherein said target nucleic acid sequence is genomic DNA, cDNA, product of a polymerase chain reaction, expressed sequence tag, mRNA or structural RNA.

62. (New Claim) A method of generating a set of oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) robotically synthesizing a plurality of synthetic oligonucleotides having at least some of said nucleobase sequences; and

c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled real-time polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

63. (New Claim) A method of generating a set of oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence comprising:

a) evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria;

b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled real-time polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

64. (New Claim) A method of generating a set of oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to defined criteria;

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled real-time polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

65. (New Claim) A method of generating a set of oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence, comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) choosing an oligonucleotide chemistry;

c) robotically synthesizing a set of synthetic oligonucleotides having said nucleobase sequences of step a) and said oligonucleotide chemistry of step b);

d) robotically assaying said set of synthetic oligonucleotides of step c) for a physical, chemical or biological activity by computer-controlled real-time polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay; and

e) selecting a subset of said set of synthetic oligonucleotides of step c) having a desired level of physical, chemical or biological activity in order to generate said set of compounds.

66. (New Claim) A method of generating a set of oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence, comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) choosing an oligonucleotide chemistry;

c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) and the oligonucleotide chemistry of b) according to defined criteria, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;

d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step c) and said oligonucleotide chemistry of step b);

e) robotically assaying said set of synthetic oligonucleotides of step (d) for a physical, chemical or biological activity by computer-controlled real-time polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay; and

f) selecting a subset of said set of synthetic oligonucleotides of step d) having a desired level of physical, chemical or biological activity in order to generate said set of oligonucleotides.

67. (New Claim) A method of generating a set of oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties.

68. (New Claim) The method of claim 67 wherein said target nucleic acid sequence is genomic DNA, cDNA, product of a polymerase chain reaction, expressed sequence tag, mRNA or structural RNA.

69. (New Claim) A method of generating a set of oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence comprising:

a) evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

70. (New Claim) A method of generating a set of oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

71. (New Claim) A method of generating a set of oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence, comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) choosing an oligonucleotide chemistry;

c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) and the oligonucleotide chemistry of b) according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;

d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step c) and said oligonucleotide chemistry of step b);

e) robotically assaying said set of synthetic oligonucleotides of step (d) for a physical, chemical or biological activity; and

f) selecting a subset of said set of synthetic oligonucleotides of step d) having a desired level of physical, chemical or biological activity in order to generate said set of oligonucleotides.

72. (New Claim) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria; and

robotically assaying a plurality of synthetic oligonucleotides corresponding to least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled real-time polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

73. (New Claim) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

robotically synthesizing a plurality of synthetic oligonucleotides; and

robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled real-time polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

74. (New Claim) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

generating a library of nucleobase sequences *in silico* according to defined criteria; and

robotically assaying a plurality of synthetic oligonucleotides having said nucleobase sequences for one or more desired physical, chemical or biological properties by computer-

controlled real-time polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

75. (New Claim) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to defined criteria; and

c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled real-time polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

76. (New Claim) The method of claim 75 wherein said nucleic acid sequence is genomic DNA, cDNA, product of a polymerase chain reaction, expressed sequence tag, mRNA or structural RNA.

77. (New Claim) The method of claim 75 wherein said nucleic acid sequence is a human nucleic acid.

78. (New Claim) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

a) evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

79. (New Claim) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to least some of said plurality of virtual oligonucleotides; and

d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

80. (New Claim) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) choosing an oligonucleotide chemistry;

c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;

d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step b) and said oligonucleotide chemistry of step c);

e) robotically assaying said set of synthetic oligonucleotides of step d) for a physical, chemical or biological activity; and

f) selecting a subset of said set of oligonucleotides of step d) having a desired level of physical, chemical or biological activity.

81. (New Claim) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically assaying a plurality of synthetic oligonucleotides corresponding to least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties.

82. (New Claim) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties.

83. (New Claim) The method of claim 82 wherein said nucleic acid sequence is genomic DNA, cDNA, product of a polymerase chain reaction, expressed sequence tag, mRNA or structural RNA.

84. (New Claim) The method of claim 82 wherein said nucleic acid sequence is a human nucleic acid.

85. (New Claim) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

a) evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

86. (New Claim) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to least some of said plurality of virtual oligonucleotides; and

d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

87. (New Claim) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) choosing an oligonucleotide chemistry;

c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;

d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step b) and said oligonucleotide chemistry of step c);

e) robotically assaying said set of synthetic oligonucleotides of step d) for a physical, chemical or biological activity; and

f) selecting a subset of said set of oligonucleotides of step d) having a desired level of physical, chemical or biological activity.

88. (New Claim) A process for validating the function of a gene or the product of said gene comprising:

generating *in silico* a library of nucleobase sequences targeted to said gene; and

robotically assaying a plurality of synthetic compounds having at least some of said nucleobase sequences for effects on biological function.

89. (New Claim) A process for validating the function of a gene or the product of said gene comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to defined criteria; and

c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for effects on biological function.

90. (New Claim) A process for validating the function of a gene or the product of said gene comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) robotically synthesizing a plurality of synthetic oligonucleotides having at least some of said nucleobase sequences; and

c) robotically assaying said plurality of synthetic oligonucleotides for effects on biological function.

91. (New Claim) A process for validating the function of a gene or the product of said gene comprising:

a) evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria;

b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

c) robotically assaying said plurality of synthetic oligonucleotides for effects on biological function.

92. (New Claim) A process for validating the function of a gene or the product of said gene:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to defined criteria;

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

d) robotically assaying said plurality of synthetic oligonucleotides for effects on biological function.

93. (New Claim) A process for validating the function of a gene or the product of said gene comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) choosing an oligonucleotide chemistry;

c) robotically synthesizing a set of synthetic oligonucleotides having said nucleobase sequences of step a) and said oligonucleotide chemistry of step b);

d) robotically assaying said set of synthetic oligonucleotides of step c) for effects on biological function; and

e) selecting a subset of said set of synthetic oligonucleotides of step c) having a desired level of biological activity in order to generate said set of compounds.

94. (New Claim) A process for validating the function of a gene or the product of said gene comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) choosing an oligonucleotide chemistry;

c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) and the oligonucleotide chemistry of b) according to defined criteria, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;

d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step c) and said oligonucleotide chemistry of step b);

e) robotically assaying said set of synthetic oligonucleotides of step d) for effects on biological function; and

f) selecting a subset of said set of synthetic oligonucleotides of step d) having a desired level of biological activity in order to generate said set of oligonucleotides.

95. (New Claim) A process for validating the function of a gene or the product of said gene comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for effects on biological function.

96. (New Claim) A process for validating the function of a gene or the product of said gene comprising:

a) evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

c) robotically assaying said plurality of synthetic oligonucleotides for effects on biological function.

97. (New Claim) A process for validating the function of a gene or the product of said gene:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

d) robotically assaying said plurality of synthetic oligonucleotides for effects on biological function.

98. (New Claim) A process for validating the function of a gene or the product of said gene comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) choosing an oligonucleotide chemistry;

c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) and the oligonucleotide chemistry of b) according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;

d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step c) and said oligonucleotide chemistry of step b);

e) robotically assaying said set of synthetic oligonucleotides of step d) for effects on biological function; and

f) selecting a subset of said set of synthetic oligonucleotides of step d) having a desired level of biological activity in order to generate said set of oligonucleotides.

99. (New Claim) A method of defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid sequence comprising:

evaluating *in silico* a plurality of virtual compounds according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically synthesizing a plurality of synthetic compounds corresponding to said plurality of virtual compounds.

100. (New Claim) A method of generating a set of oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides.

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101. (New Claim) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically synthesizing a plurality of synthetic oligonucleotides corresponding to least some of said virtual oligonucleotides.

102. (New Claim) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) evaluating in silico a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides.

103. (New Claim) A process for validating the function of a gene or the product of said gene comprising:

a) generating a library of nucleobase sequences *in silico* according to defined criteria;

b) evaluating in silico a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides.

REMARKS

Claims 1-54 have been cancelled without prejudice to their presentation in another application. New claims 55-103 have been added herein. Upon entry of the present Amendment, claims 55-103 will be pending.

The paragraph beginning at page 47, line 4 of the specification has been corrected to remove the embedded hyperlink as suggested in the Office Action.

I. The Claimed Inventions Are Novel

A. The Gilbert Reference

Claims 3, 4, 6-20, 23, 24, 26-40 and 47-54 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by EPO 0,514,927 (hereinafter, the "Gilbert reference"). Although Applicants disagree with the assertions in the Office Action and maintain that the claimed inventions are novel, solely to advance prosecution of the present application, Applicants have cancelled the rejected claims in favor of new claims 55-103.

New claims 59, 67-71, 78-87 and 95-103 recite that the defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence. The Gilbert reference does not teach such defined criteria. Thus, claims 59, 67-71, 78-87 and 95-103 are novel in view of the Gilbert reference.

New claims 55-58, 60-66 and 72-77 recite that assaying is performed by computer-controlled real-time polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay. The Gilbert reference does not teach, nor is it alleged to teach, computer-controlled enzyme-linked immunosorbent assay. In contrast to the assertions in the Office Action, the Gilbert reference also does not teach computer-controlled real-time polymerase chain reaction. The Office Action asserts that the Gilbert reference teaches PCR at page 19, lines 2-4 and erroneously implies that it is computer-controlled real-time PCR. Applicants teach a representative computer-controlled real-time PCR in, for instance, Example 10C of the specification. In contrast, when taken in full context, the Gilbert reference simply reports that PCR can be used to generate a sequence that spans a particular repeat region of a nucleic acid, where such a repeat region is not amenable to sequencing via the system disclosed therein. There is no teaching in the Gilbert reference that the PCR mentioned therein is computer-controlled real-time PCR. Further, the PCR reported in the Gilbert reference simply provides missing sequence information and is not used to assay for a physical, chemical, or biological property of a synthetic compound. Thus, claims 55-58, 60-66 and 72-77 are novel in view of the Gilbert reference.

New claims 88-94 recite assaying for effects on biological function. Nowhere does the Gilbert reference teach assaying synthetic compounds for effects on biological function. Thus, claims 88-94 are novel in view of the Gilbert reference.

Accordingly, in view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

B. The Hubbell Reference

Claims 3, 4, 6-17, 19, 20, 23, 24, 26-37, 39, 40 and 47-54 stand rejected under 35 U.S.C. §102(b) and §102(e) as allegedly being anticipated by U.S. Patent No. 5,571,639 (hereinafter, the "Hubbell reference"). Although Applicants disagree with the assertions in the Office Action and maintain that the claimed inventions are novel, solely to advance prosecution of the present application, Applicants have cancelled the rejected claims in favor of new claims 55-103.

New claims 55-58, 60-66 and 72-77 recite that assaying is performed by computer-controlled real-time polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay. Original claims 18 and 38, which recited the same language, were not rejected. Thus, claims 55-58, 60-66 and 72-77, which recite the same language, are novel in view of the Gilbert reference.

New claims 59, 67-71, 78-87 and 95-103 recite that the defined criteria for *in silico* evaluation of virtual compounds is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence. The Hubbell reference does not teach *in silico* evaluation of virtual compounds using such defined criteria. Thus, claims 59, 67-71, 78-87 and 95-103 are novel in view of the Hubbell reference.

New claims 88-94 recite robotically assaying said plurality of synthetic oligonucleotides for effects on biological function. Nowhere does the Hubbell reference teach such an assaying step. Indeed, the passages identified in the Office Action (column 3, line 51 through column 5, line 5, and column 18, line 15 through column 19, line 26) do not teach any assays for biological function. The first passage simply reports a computerized system for forming and analyzing arrays of biological materials using a chip. Indeed, the only analyzing that is reported in the first passage is binding between the labeled receptor and the substrate on the chip. The second passage merely reports scanning techniques that can be used to analyze the chip. Neither of these passages teaches robotically assaying a plurality of synthetic oligonucleotides for effects on biological function. Thus, claims 88-94 are novel in view of the Hubbell reference.

Accordingly, in view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

II. The Claimed Inventions Are Not Obvious

Claims 3, 4, 6-20, 23, 24, 26-40 and 47-54 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over the combination of the Gilbert reference and Nickerson *et al.*, *Proc. Natl. Acad. Sci. USA*, **1990**, *87*, 8923-8927 (hereinafter, the "Nickerson reference"). Although Applicants disagree with the assertions in the Office Action and maintain that the claimed inventions are novel and not obvious, solely to advance prosecution of the present application, Applicants have cancelled the rejected claims in favor of new claims 55-103. The Office Action mistakenly asserts that it would have been *prima facie* obvious for one skilled in the art to perform the methods of the Gilbert reference additionally with the methods of the Nickerson reference. Applicants traverse the rejection and respectfully request reconsideration because there is no motivation to combine the cited references.

As a preliminary matter, new claims 59, 67-71, 78-87 and 95-103 recite that the defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence. Neither the Gilbert reference nor Nickerson reference teach such defined criteria. Thus, claims 59, 67-71, 78-87 and 95-103 are not obvious in view of the combination of the Gilbert and Nickerson references.

In addition, new claims 88-94 recite assaying for effects on biological function. Nowhere does the Gilbert reference or Nickerson reference teach assaying synthetic compounds for effects on biological function. Thus, claims 88-94 are novel in view of the combination of the Gilbert and Nickerson references.

New claims 55-58, 60-66 and 72-77 recite that assaying is performed by computer-controlled real-time polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay. In establishing a *prima facie* case of obviousness under 35 U.S.C. §103, it is incumbent upon the Examiner to provide a reason why one of ordinary skill in the art would have

been led to modify a prior art reference or to combine reference teachings to arrive at the claimed invention. *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. Int. 1985). To this end, the requisite motivation must stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and not from appellants' disclosure, see for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd. Pat. App. Int. 1992). In this respect, the following quotation from *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993), is noteworthy:

> Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that would **impel** one skilled in the art to do what the patent applicant has done. (citations omitted; emphasis added)

Significantly, the Office Action identifies no "motivating force" that would "impel" persons of ordinary skill to modify the respective teachings of the cited references and achieve the claimed invention. The only motivation identified in the Office Action for combining the Gilbert and Nickerson references is allegedly found in the "Materials And Methods" section of the Nickerson reference wherein an automated robotic workstation is reported. This alleged motivation, however, in no way would lead one skilled in the art to combine the teachings of the cited references. The Gilbert method is directed to automated nucleic acid sequencing. One skilled in the art would not be motivated to modify the method of automated nucleic acid sequencing reported in the Gilbert reference let alone add a peripheral method involving an automated ELISA assay, as reported in the Nickerson reference. It is not even clear what benefit is gained by using such an ELISA assay in conjunction with an automated nucleic acid sequencing method.

Applicants further note that "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). Under this standard, none of the prior art of record, alone or in any proper combination, discloses or suggests the present invention as defined by the new claims. This is not to say that it is impossible to combine selected elements of several references to show the obviousness of an invention, however, there still must be a "suggestion or motivation in the prior art to make the selection." *In re Gorman*, 18 U.S.P.Q.2d 1885, 1888 (Fed. Cir. 1991) (claim held obvious in view of combined teachings of references showing elements for same purpose as claimed invention).

In view of the foregoing, the claimed inventions are not obvious in view of the combination of the Gilbert and Nickerson references. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

III. The Claims Are Clear And Definite

Claims 3, 4, 6-20, 23, 24, 26-40 and 47-54 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. The Office Action asserts that the claims are vague and indefinite because the preambles cite the defining or generating of compounds that modulate expression, are amendable to antisense binding, or for validating the function of a gene or gene product without any steps that are directed to the same. Applicants traverse the rejection and respectfully request reconsideration because the new claims are clear and definite.

New claims 55-71, 99 and 100 recite methods of defining a set of compounds or generating a set of oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of the compounds or oligonucleotides with the target nucleic acid sequence. Each of these claims recites, *inter alia*, a step involving a robotic assay of synthetic compounds or oligonucleotides that can, for example, provide data regarding binding of the compounds or oligonucleotides with the target nucleic acid sequence, which is indicative of modulating the expression of the target nucleic

acid sequence. New claims 72-87, 101 and 102 recite methods of identifying one or more nucleic acid sequences amenable to antisense binding. Again, each of these claims recites, *inter alia*, a step involving a robotic assay of oligonucleotides that provides data regarding binding of the oligonucleotides with the target nucleic acid sequence. New claims 88-98 and 103 recite methods for validating the function of a gene or gene product. Each of these claims recites, *inter alia*, robotically assaying a plurality of synthetic compounds or oligonucleotides for effects on biological function, which can validate or invalidate the function of a gene or gene product. Thus, every pending claim has at least one step that is directed to modulation of expression by binding, antisense binding, or gene function validation.

The Office Action also asserts that the phrase "defined criteria" is excessively broad and does not appear to be related to modulation of expression, etc. The phrase "defined criteria" appears in the claims in the context of "generating" and "evaluating." In regard to, for example, generating compounds "according to defined criteria," Applicants teach at, for example, page 9, line 19 through page 16, line 25 and page 23, line 29 through page 32, line 3 of the specification numerous criteria for target nucleic acid selection, assembly of target nucleic acid sequence and generation of compounds having a particular chemistry. In regard to, for example, evaluating compounds "according to defined criteria," Applicants teach at, for example, page 16, line 26 through page 22, line 2 of the specification numerous criteria including thermodynamic properties, target accessibility, targeting to functional regions of target nucleic acid sequence, and uniform distribution to target nucleic acid sequence. Applicant respectfully points out that the description of the invention is the role of the specification, not the claims. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 U.S.P.Q.2d 1081 (Fed. Cir. 1986). In addition, the amount of detail required to be included in the claims is not to be viewed in the abstract but in conjunction with the specification. *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 225 U.S.P.Q. 634 (Fed. Cir. 1985). As such, the specification contains numerous examples of "defined criteria" used in connection with the generation and evaluation steps recited in the claims.